REMARKS

Claims 1-106 have been canceled without prejudice, and new claims 107-119 have been added. Claims 107-119 are now pending for the Examiner's consideration.

Claims 107-119 have been added to recite a particular embodiment of the invention. The new claims are supported by claims 1-106 as filed, and no new matter is added.

Applicant respectfully requests favorable consideration of the pending claims.

1. Claims 1, 2, 4, 8-16, 18-43, 45-56, 59, 61-77 and 92 were rejected under 35 U.S.C. § 102(b) as being anticipated by PCT Publication No. WO 01/37820 to Shenoy et al. ("Shenoy '820"), for the reasons set forth on pages 3-4 of the Office Action. These claims have been canceled without prejudice, and the rejection is moot. For the reasons that follow, Applicant believes the rejection is not applicable to new claims 107-119.

New claims 107-119 recite a specific compound, 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate. As Shenoy does not disclose formulations of the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide, the rejection does not apply to the currently pending claims. Accordingly, Applicant respectfully requests that the rejection under § 102(b) over Shenoy '820 be withdrawn.

2. Claims 1, 2, 4, 8-16, 18-43, 45-56, 59, 61-77, 79, 80, 83-85, 87 and 92 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Application Publication No. 2003-0130280 to O'Farrell et al. ("O'Farrell '280"), for the reasons set forth on pages 4-5 of the Office Action. These claims have been canceled without prejudice, and the rejection is moot. For the reasons that follow, Applicant believes the rejection is not applicable to new claims 107-119.

O'Farrell et al. was filed October 28, 2002, claiming priority to U.S. Provisional Application No. 60/330,623 ("the '623 Provisional"), filed October 26, 2001. Since the present application claims priority to U.S. Provisional Application No. 60/421,133, filed September 10, 2002, only the disclosure of the O'Farrell priority document, the '623 Provisional, is available as prior art. The '623 Provisional discusses formulations generally, and describes a co-solvent formulation not relevant to the present claims, but does not disclose formulations having the concentration ranges recited in the present claims. In particular, Tables 1-3 in paragraphs [0203] to [0205] of O'Farrell '280 were added to the specification in the U.S. regular application, but are not present in the '623 Provisional. Accordingly, since the reference did not describe every element of the claimed invention before the priority date of September 10, 2002, there can be no anticipation. Applicant respectfully requests that the rejection under § 102(e) over O'Farrell '280 be withdrawn.

3. Claims 79-85 and 87 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Shenoy '820, for the reasons set forth on pages 5-7 of the Office Action. These claims have been canceled without prejudice, and the rejection is moot. For the reasons that follow, Applicant believes the rejection is not applicable to new claims 107-119.

The Shenoy '820 reference is directed to formulations of "an ionizable substituted indolinone" which is "necessarily substituted on the pyrrole moiety with one or more hydrocarbon chains which themselves are substituted with at least one polar group" (see WO 01/37820 Abstract). The compound recited in the current claims has three substituents on the pyrrole group: two methyl groups and an amide. It is not substituted with a hydrocarbon chain which is further substituted with a polar group. As noted throughout the Shenoy '820 specification, the preferred compound, and the only compound for which examples are shown, is 3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid (Compound IV; see page 29), a compound which has a propionic acid substituent on the pyrrole ring. This important structural difference results in a compound which is an acidic, ionizable, hydrophobic compound (pKa 5.02; see page 226, lines 4-5). The aqueous solubility of the free acid compound ranges from 0.0024 to 1.6 mg/mL at pHs of from 6.0 to 9.0 (Table 4, page 225), and the highest solubility reported is 17-25 mg/mL for the sodium salt at a pH of 8.6-8.9. It is these properties (hydrophobic, ionizable) which drive

the formulation development (see page 224, lines 13-14, and page 226, lines 11-15), which relies on the sodium salt or an in-situ sodium salt formation (see Example 3).

In contrast, the compound recited in the present claims is a weakly basic compound (pKa 8.95) with relatively good water solubility. A direct comparison of the aqueous solubility of the Shenoy '820 compound and the compound recited in the present claims can be found in Table 1 of *J. Med. Chem.* 2003, 46, 1116-1119, a copy of which is attached hereto for the Examiner's reference. As the Table shows, under the conditions described in footnote (b), the Shenoy '820 compound (Compound 5b) has a pH 2 solubility of less than 5 μg/mL compared to 2582 μg/mL for the compound of the present claims (Compound 12b). At pH 6, the solubilities are 18 μg/mL and 364 μg/mL, respectively. The dramatically improved aqueous solubility eliminates the need to rely on an in-situ salt formation strategy as in the compound of Shenoy '820. Given the differences between the compounds, one would not look to the teachings of Shenoy '820, directed to formulations to enhance the solubility of hydrophobic, ionizable compounds, to provide a formulation for 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate, which has good aqueous solubility.

Accordingly, Applicant respectfully requests that the rejection be reconsidered and withdrawn.

4. Claims 81 and 82 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Application Publication No. 2003/0130280 to O'Farrell et al. ("the O'Farrell '280 publication"), for the reasons set forth on pages 7-8 of the Office Action. The O'Farrell '280 publication is available as 103(a) prior art only under § 102(e). However, the subject matter of the O'Farrell '280 publication and the claimed invention were, at the time the claimed invention was made, owned by the same person (Pfizer). Thus, under 35 U.S.C. § 103(c), the O'Farrell '280 publication is disqualified as 103(a) prior art, and Applicant respectfully requests that the rejection be withdrawn.

5. Claims 1, 2, 4, 8-11, 68-77 and 92 were rejected under 35 U.S.C. § 103(a) as being unpatentable over International Publication No. WO 01/45689 to Lipson et al. ("Lipson '689"), for the reasons set forth on pages 8-9 of the Office Action. These claims have been

canceled without prejudice, and the rejection is moot. For the reasons that follow, Applicant believes the rejection is not applicable to new claims 107-119.

Lipson '689 is directed to methods of treatment of cell proliferative disorders using certain indolinone compounds. The Examiner argues that Lipson '689 teaches a solid formulation comprising all of the elements recited in the present claims, with the exception of certain weight percentages. Applicant respectfully disagrees. Lipson '689 discloses 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide as compound 16 on page 16, but fails to disclose the compound as an L-malate salt. On page 38, line 35, Lipson '689 discloses that "Many of the PTK modulating compounds of the invention may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc." (page 38, lines 13-15). Although "many" compounds of Lipson '689 can be provided as salts, Lipson fails to teach that the specific compound 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide can, or cannot, be provided as a salt, and if so, which of the many recited salts. Further, although Lipson '689 lists various formulation ingredients, it fails to indicate which of the various recited ingredients should be chosen, and in what amounts. It cannot be obvious to make the required ingredient selections and amounts, absent any guidance in Lipson '689 for making the many selections.

The Examiner argues that determination of the therapeutically effective amount of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide L-malate would be obvious, and a matter of routine selection. However, as is shown in the present specification, selection of the L-malate salt and the particularly claimed amount of the recited compound result in unexpected advantages. In particular, a formulation is shown on pages 91 and 92 using the free base compound and in an amount of 65% by weight. As shown on page 92, this formulation results in a composition having a bulk density of only 0.44 kg/L. Low bulk density is particularly disadvantageous in a solid formulation, as the composition is difficult to handle and capsules are difficult to fill. Replacing the free base with the L-malate salt but maintaining a high weight percent of the active ingredient (75%; see Comparative Example on page 95) results in a composition

having undesirable sticking problems in the manufacturing process, again making capsule formation difficult.

In contrast, formulations of the present invention using the L-malate salt of 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide and in amounts of 5 to 60% by weight results in compositions having bulk densities approximately 50% greater (0.64 to 0.67 kg/L; Examples 3 and 4) and displaying no sticking problems (Comparative Example). It would not have been obvious to select from the disclosure of Lipson '689 the L-malate salt rather than the free base (or another salt) and further to select the weight percentage of the active ingredient in order to produce a composition having improved bulk density and processing characteristics. Thus, Applicant believes the present claims would not have been obvious over the Lipson '689 disclosure, and respectfully request that the rejection under § 103(a) be reconsidered and withdrawn.

6. Claims 1, 2, 4, 8-11, 68-77 and 92 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Application Publication No. 2003/0069298 to Hawley et al. ("Hawley '298"), for the reasons set forth on pages 9-10 of the Office Action. These claims have been canceled without prejudice, and the rejection is moot. For the reasons that follow, Applicant believes the rejection is not applicable to new claims 107-119.

The Examiner acknowledges that Hawley '298 does not teach the specific weight percentages recited in the claims. Thus, there can be no anticipation, and Applicant respectfully requests that the rejection be withdrawn.

7. Claims 1, 2, 4, 8-11, 68-77 and 92 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Application Publication No. 2002/0156292 to Tang et al. ("Tang '292"), for the reasons set forth on pages 10-11 of the Office Action. These claims have been canceled without prejudice, and the rejection is moot. For the reasons that follow, Applicant believes the rejection is not applicable to new claims 107-119.

The Examiner acknowledges that Tang '292 does not teach the specific weight percentages recited in the claims. Thus, there can be no anticipation, and Applicant respectfully requests that the rejection be withdrawn.

Applicant believes all claims are now in condition for allowance. Should there be any issues that have not been addressed to the Examiners satisfaction, Applicant invites the Examiner to contact the undersigned attorney.

If any fees other than those submitted herewith are due in connection with this response, including the fee for any required extension of time (for which Applicant hereby petitions), please charge such fees to Deposit Account No. 500329.

Respectfully submitted,

Date: August 4, 2006

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Discovery of 5-[5-Fluoro-2-oxo-1,2-dihydroindol-(3*Z*)-ylidenemethyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxylic Acid (2-Diethylaminoethyl)amide, a Novel Tyrosine Kinase Inhibitor Targeting Vascular Endothelial and Platelet-Derived Growth Factor Receptor Tyrosine Kinase

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Received September 24, 2002

Abstract: To improve the antitumor properties and optimize the pharmaceutical properties including solubility and protein binding of indolin-2-ones, a number of different basic and weakly basic analogues were designed and synthesized. 5-[5-Fluoro-2-oxo-1,2-dihydroindol-(3*Z*)-ylidenemethyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide (**12b** or SU11248) has been found to show the best overall profile in terms of potency for the VEGF-R2 and PDGF-Rβ tyrosine kinase at biochemical and cellular levels, solubility, protein binding, and bioavailability. **12b** is currently in phase I clinical trials for the treatment of cancers.

Introduction. Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors have been well validated as targets for the treatment of cancers because of their critical roles in tumor growth and suvival via autocrine and paracrine loops.[1−4] In this regard, both receptor tyrosine kinases (RTKs) have been found to be expressed on the tumor cells and to directly affect tumor cell proliferation (e.g., VEGF receptor in melanoma and PDGF receptor in gliomas).[1] In addition, both RTKs have been found to play prominent roles in tumor angiogenesis by participating in the transmission of proliferation, migration, differentiation, and survival signals between tumor cells and endothelial cells.[2−4] Thus, simultaneous inhibition of both endothelial growth factor receptor-2 (VEGF-R2) and platelet-derived growth factor receptor-β (PDGF-Rβ) might be expected to show better antitumor activity than by inhibiting only one of these RTKs. In the past several years, we have taken two indolin-2-ones, **5a** (SU5416) (VEGF-R selective inhibitor[5]) and **5b** (SU6668) (a potent and selective PDGF-Rβ tyrosine kinase inhibitor) (Table 1), to clinical trials for the treatment of cancers.[6,7] However, their low solubility and/or high protein binding properties were considered to be potential liabilities. In this study, efforts have been focused on finding an indolin-2-one analogue that shows potent and broad inhibitory activity against both VEGF-R2 and PDGF-Rβ and has good pharmaceutical properties with regard to solubility and protein binding. We report here the design, synthesis, and structure−activity relationship that led to the discovery of **12b** (Table 1),[8] a potent tyrosine kinase inhibitor targeting VEGF-R2 and PDGF-Rβ.

Chemistry. To broaden the kinase selectivity spectrum of indolin-2-one for both VEGF-R2 and PDGF-Rβ and to optimize the pharmaceutical properties including solubility and protein binding, diversification at the C-4′ position on the pyrrole ring of **5a** has been explored. We learned from the past structure−activity relationship studies on indolin-2-ones that modifications at the C-4′ position could lead to compounds with different kinase inhibition profiles for VEGF-R2 and PDGF-Rβ. In this regard, neutral **5a**[12] has been found to be a potent and selective inhibitor for VEGF-R2 while acidic **5b**[6] was found to be such for PDGF-Rβ. On the other hand, the cocrystal structure of **5b** in the catalytic domain of the FGF-R1 kinase,[6] a kinase that has high amino acid sequence homology for the ATP-binding pocket to VEGF-R2, revealed that the substitution at the C-4′ position on the pyrrole ring is positioned close to the opening of the binding pocket and could be exposed to solvent. Thus, substitution at this position might serve as a handle for improving pharmaceutical properties of the indolin-2-ones. In this study, various basic side chains have been introduced at the C-4′ position of **5a** to broaden the kinase inhibition spectrum and to improve pharmaceutical properties (particularly solubility) of indolin-2-ones. First, we introduced the aminoalkyl functionality in **5a** (**5c** in Scheme 1). Starting from **1**,[7] **5c** was synthesized by amidation with *N*-methylpiperazine, reduction of the amide functionality, formylation, and condensation with the indolin-2-one. Further diversification at the C-4′ position on the pyrrole ring of **5a** was also explored by introducing soluble aminoalkylamide functionalities as depicted in Scheme 2 (**12a−j**). The key intermediate **10** was prepared from commercially available 3-oxobutyric acid *tert*-butyl ester (**6**) by condensing with sodium nitrite in acetic acid, reductive cyclization with 3-oxobutyrate ethyl ester, hydrolytic decarboxylation and formylation, and base hydrolysis of the ethyl ester of **9**. Condensation of **10** with different indolin-2-ones afforded **11**, which upon amidation with different amines was converted to **12a−j**. Most of the amines used are commercially available except the amines (Scheme 3) for synthesizing **12g** and **12j**.

Results and Discussion. The biological activities of the synthesized compounds were first evaluated in biochemical assays measuring tyrosine phosphorylation of VEGF-R2, PDGF-Rβ, fibroblast growth factor receptor-1 (FGF-R1), and epidermal growth factor receptor (EGF-R) as described previously.[6,7] Potent and selective inhibitors against VEGF-R2 and PDGF-Rβ were subsequently tested for their kinase inhibitory activity in 3T3 cells, inhibitory activity against ligand-induced cellular proliferation (as measured by BrdU incorporation in 3T3 cells), cellular cytotoxicity, and solubility at pH 2 and 6 (Table 1).

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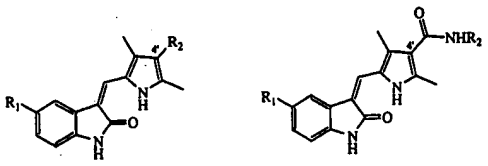
10.1021/jm0204183 CCC: $25.00
Published on Web 03/05/2003

Table 1. In Vitro Kinase Inhibitory Activities and Solubility

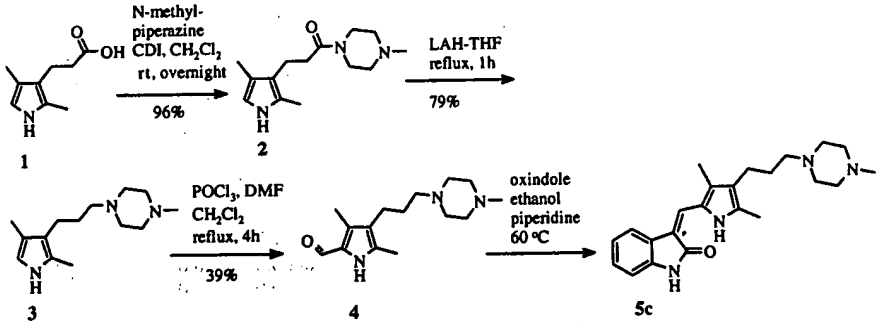


5 12

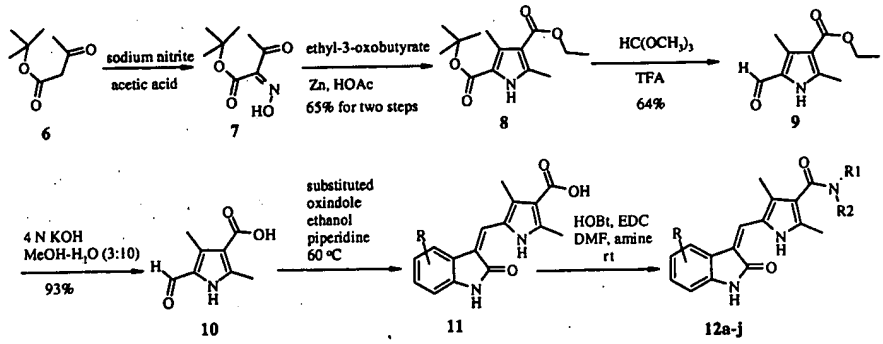
			biochemical activity against kinases IC_{50},[a] μM				cellular kinase activity in 3T3 cell IC_{50},[a] μM		PDGF-induced BrdU incorporation		solubility,[b] μg/mL	
compd	R1	R2	VEGF-R2	PDGF-Rβ	FGF-R1	EGF-R	VEGF	PDGF	IC_{50},[a] μM	cytotoxicity LD_{50},[a] μM	pH 2	pH 6
5a	H	H	1.23	22.9	>100	>100	1.04	20.3	4.05	>50	<1	<1
5b	H	$(CH_2)_2COOH$	2.4	0.060	3.00	>20	1–2	0.1–1.0	16	>50	<5	18
5c	H	$(CH_2)_3N(CH_2CH_2)_2NCH_3$	0.3	0.060	4.20	>20	*d*	*d*	0.20	>50	*d*	*d*
12a	H	$(CH_2)_2N(C_2H_5)_2$	0.050	0.017	0.88	>20	0.05–0.5	0.1–1.0	<0.07	>50	3022	511
12b	F	$(CH_2)_2N(C_2H_5)_2$	0.080	0.0020	2.90	>20	0.005–0.05	0.01	0.008	48.9	2582	364
12c	Cl	$(CH_2)_2N(C_2H_5)_2$	0.027	0.0030	0.17	>20	0.005–0.05	0.01–0.1	<0.07	15.6	3259	186
12d	Br	$(CH_2)_2N(C_2H_5)_2$	0.032	0.0050	0.73	10	0.005–0.05	0.01–0.1	<0.07	16.3	1299	101
12e	F	$(CH_2)_2N(CH_3)_2$	0.080	0.0005	1.60	>20	0.005–0.05	0.01–0.1	0.015	48.5	3012	75
12f	F	$(CH_2)_2$-pyrrolidin-1-yl	0.060	0.0010	3.90	>20	0.005–0.05	0.01–0.1	<0.07	49	3319	9
12g	F	$CH_2CH(CH_2CH_2)_2N-CH_3$	0.025	0.0030	0.20	*d*	0.04	0.02	0.030	38	>250	>250
12h	F	$(CH_2)_2$-morpholin-4-yl	0.090	0.0020	2.60	>20	0.05	*d*	0.037	>50	2945	0.3
12i	F	CH_2-pyridin-4-yl	<0.16	0.0010	3.10	>20	0.005–0.05	0.01–0.1	0.080	>50	486	<LD[c]
12j	F	$(CH_2)_2$-triazol-1-yl	0.085	0.010	17.1	>20	0.05–0.5	0.1–1.0	0.19	>50	2	6

[a] IC_{50} and LD_{50} values were determined by at least two separate tests and reported as mean values. [b] Solubility of the compounds was determined in 20 mM buffered solutions (pH 2, KCl/HCl; pH 6, phosphate) after shaking for 24 h at 22 °C. Data presented are from a single determination or an average of two determinations. [c] LD = limit for detection. [d] Not tested.

Scheme 1. Synthesis of **5c**



Scheme 2. Synthesis of 4′-Carboxamide Analogues of **5a**



It is interesting to note that converting the carboxylate group of **5b** into an amino group (**5c**) enhances the inhibitory activity for VEGF-R2 (8-fold) while retaining the potency against PDGF-Rβ kinase (Table 1). The difference in potency observed between inhibition of PDGF-induced BrdU incorporation and inhibition of cellular kinase activity for **5b** might be related to its poor solubility (Table 1). The SAR implied that a basic analogue of **5a** has shown broader kinase inhibitory activity against both VEGF-R2 and PDGF-Rβ than neutral (i.e. **5a**-VEGF-R-selective inhibitor[9]) and an acid analogue (i.e., **5b**-PDGF-Rβ-selective inhibitor), confirming that the kinase selectivity could be affected by a substitent at the C-4′ position.

Being encouraged by the above results, we extensively explored other possibilities for diversification at the C-4′ position and found that the readily accessible **12** showed the most promise. **12a–d** exhibited even more potent

Scheme 3. Synthesis of Amines for **12g** and **12j**

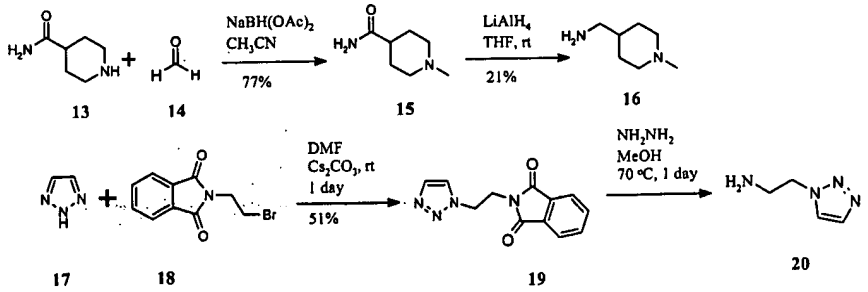


Table 2. Effects of Protein Binding on Cellular Potency[a]

	PDGF-induced BrdU incorporation in 3T3 cells, IC_{50} (μM)				
compd	at 0% BSA	at 0.1% BSA	at 0.5% BSA	at 1% BSA	at 5% BSA
5b	0.3	9.5	16	36	49
12b	<0.007	<0.007	<0.007	0.008	0.083

[a] BSA = bovine serum albumin.

inhibitory activity against VEGF-R2 and PDGF-Rβ in biochemical and cellular assays (Table 1). Specifically, compared to **5b**, **12b** is about 30-fold more potent against VEGF-R2 and PDGF-Rβ in biochemical assays, over 10-fold more potent in cellular kinase assays, and significantly more soluble under neutral (20-fold) and acidic (>500-fold) conditions. Among **12a–d**, **12a** is markedly less potent in inhibiting PDGF-Rβ phosphorylation in biochemical and cellular assays. Different halogen substitutions had little effect on the biochemical activities against VEGF-R2 and PDGF-Rβ but affected the cytotoxicity profiles. For example, the bulkier Cl and Br substitutions (**12c** and **12d**) show some extent of cytotoxicity when compared to the F analogue (**12b**) (Table 1). Therefore, diversification on **12b** has been further explored.

Surprisingly, replacing the diethylamine in **12b** by either dimethylamine (**12e**) or pyrrolidine (**12f**) markedly reduced solubility at pH 6 (from 364 to 75 or 9 μg/mL, respectively), while the in vitro activities were similar (Table 1). The more basic *N*-methylpiperidine group (which significantly increased solubility of the quinazoline-based VEGF-R2/EGF-R inhibitor (4-bromo-2-fluorophenyl)[6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]amine or ZD6474)[10] also improved the solubility of **12g**. However, this substitution increased cytotoxicity and decreased metabolic stability because of N-demethylation (data not shown). The much less basic morpholino analogue **12h** is also much less soluble at pH 6, though it has good solubility at pH 2. The basic heteroaromatic analogues **12i** and **12j** have generally poor solubility and sometimes reduced cellular potency (**12j** in Table 1).

To assess the protein binding properties for **5b** and **12b**, cellular IC_{50} values were measured in the presence or absence of serums. Compared to **5b**, the cellular potency of **12b** against PDGF-induced proliferation is less likely to be affected by the presence of serum protein (Table 2). In this regard, **12b** was still a very potent inhibitor of PDGF-Rβ while **5b** became inactive in the presence of a high level of serum.

In conclusion, **12b** possesses the best overall profile in terms of inhibitory potency against the VEGF-R2 and PDGF-Rβ targets in biochemical and cellular assays, solubility under both neutral and acidic conditions, and protein binding properties. Additional kinase selectivity study revealed that **12b** is also a good inhibitor of KIT and FLT-3.[13] Furthermore, **12b** also had very good oral bioavailability, was highly efficacious in a number of preclinical tumor models, and was well tolerated at efficacious doses.[8] It is currently in clinical phase I trials for the treatment of cancers.

Supporting Information Available: Synthesis of **12b**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Cherrington, J. M.; Strawn, L. M.; Shawver, L. K. New paradigms for the treatment of cancer: the role of anti-angiogenesis agents. In *Advances in Cancer Research*, 1st ed.; Klein, G., Van de Woude, G. F., Eds.; : Academic Press: San Diego, CA, 2000; Vol. 70, pp 1–38.

(2) Gale, N. W.; Yancopoulos, G. D. Growth factors acting via endothelial cell-specific receptor tyrosine kinases: VEGFs, angiopoietins, and ephrins in vascular development. *Genes Dev.* **1999**, *13*, 1055–1066.

(3) Ferrara, N. VEGF: an update on biological and therapeutic aspects. *Curr. Opin. Biotechnol.* **2000**, *11*, 617–624.

(4) Rosenkranz, S.; Kazlauskas, A. Evidence for distinct signaling properties and biological responses induced by the PDGF receptor alpha and beta subtypes. *Growth Factors* **1999**, *16*, 201–216.

(5) Sun, L.; Tran, N.; Tang, T.; App, H.; Hirth, P.; McMahon, G.; Tang, C. Synthesis and biological evaluations of 3-substituted indolin-2-ones: a novel class of tyrosine kinase inhibitors that exhibit selectivity towards particular receptor tyrosine kinases. *J. Med. Chem.* **1998**, *41* (14), 2588–2603.

(6) Laird, A. D.; Vajkoczy, P.; Shawver, L. K.; Thurnher, A.; Liang, C.; Mohammadi, M.; Schlessinger, J.; Ullrich, A.; Hubbard, S. R.; Blake, R. A.; Fong, A. T.; Strawn, L. M.; Sun, L.; Tang, C.; Hawtin, R.; Tang, F.; Shenoy, N.; Hirth, K. P.; McMahon, G.; Cherrington, J. M. SU6668 is a potent antiangiogenic and antitumor agent that induces regression of established tumors. *Cancer Res.* **2000**, *60*, 4152–4160.

(7) Sun, L.; Tran, N.; Liang, C.; Tang, F.; Rice, A.; Schreck, R.; Waltz, K.; Shawver, L. K.; McMahon, G.; Tang, C. Design, synthesis, and evaluations of substituted 3-[(3- or 4-carboxyethylpyrrol-2-ylmethylidenyl]indolin-2-ones as inhibitors of VEGF, FGF, and PDGF receptor tyrosine kinases. *J. Med. Chem.* **1999**, *42*, 5120–5130.

(8) Mendel, D. B.; Laird, A. D.; Xin, X.; Louie, S. G.; Christensen, J. G.; Li, G.; Schreck, R. E.; Abrams, T. J.; Ngai, T. J.; Lee, L. B.; Murray, L. J.; Carver, J.; Chan, E.; Moss, K. G.; Haznedar, J. O.; Sukbuntherng, J.; Blake, R. A.; Sun, L.; Tang, C.; Miller, T.; Shirazian, S.; McMahon, G.; Cherrington, J. M. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting VEGF and PDGF receptors: Determination of a pharmacokinetic/pharmacodynamic relationship. *Clin. Cancer Res.* **2003**, *9*, 327–337.

(9) Fong, A. T. T.; Shawver, L. K.; Sun, L.; Tang, C.; App, H.; Powell, T. J.; Kim, Y. H.; Schreck, R.; Wang, X. Y.; Risau, W.; Ullrich, A.; Hirth, K. P.; McMahon, G. SU5416 is a potent and selective inhibitor of the vascular endothelial growth factor receptor (Flk-1/KDR) that inhibits tyrosine kinase catalysis, tumor vascularization, and growth of multiple tumor types. *Cancer Res.* **1999**, *59*, 99–106.

(10) Hennequin, L. F.; Stokes, E. S. E.; Thomas, A. P.; Johnstone, C.; Ple, P. A.; Ogilvie, D. J.; Dukes, M.; Wedge, S. R.; Kendrew, J.; Curwen, J. O. Novel 4-anilinoquinazolines with C-7 basic side chains: Design and structure activity relationship of a series of potent, orally active, VEGF receptor tyrosine kinase inhibitors. *J. Med. Chem.* **2002**, *45*, 1300−1312.

(11) Liao, A. T.; Chien, M. B.; Shenoy, N.; Mendel, D. B.; McMahon, G.; Cherrington, J. M.; London, C. A. Inhibition of constitutively active forms of mutant kit by multitargeted indolinone tyrosine kinase inhibitors. *Blood* **2002**, *100*, 585−593.

(12) Fong, T. A. T.; Shawver, L. K.; Sun, L.; Tang, C.; App, H.; Powell, T. J.; Kim, Y. H.; Schreck, R.; Wang, X.; Risau, W.; Ullrich, A.; Hirth, K. P.; McMahon, G. SU5416 is a potent and selective inhibitor of the vascular endothelial growth factor receptor (Flk-1/KDR) that inhibits tyrosine kinase catalysis, tumor vascularization, and growth of multiple tumor types. *Cancer Res.* **1999**, *59* (1), 99−106.

(13) Mendel, D. B.; Laird, A. D.; Xin, X.; Abrams, T. J.; Li, G.; Schreck, R. E.; Carver, J.; Louie, S. G.; Ngai, T. J.; Lee, L. B.; Nannini, M. A.; Murray, L. J.; Tang, C.; McMahon, G.; Cherrington, J. M. In vivo antitumor and mechanism of action studies of SU11248, a potent and selective inhibitor of the VEGF and PDGF receptors. Presented at the American Association for Cancer Reserch, 2002; Poster 5349.

JM0204183